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EPIDEMIOLOGIC STUDIES ON THE CAUSAL ASSOCIATION BETWEEN ENVIRONMENTAL TOBACCO SMOKE AND DISEASE: LUNG CANCER AND HEART DISEASE

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Contractor:
ToxaChemica, International, Inc.
Landow Building
Suite 1000
7910 Woodmont Ave
Bethesda, MD20814

by

Subcontractor:
Kenneth G. Brown, Inc.
P.O. Box 16608
Chapel Hill, NC 27516

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6. CONCLUSIONS FOR HAZARD IDENTIFICATION

6.1. Criteria for Causality

According to EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1986a), a Group A (known human) carcinogen designation is used "when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agents and cancer." The *Guidelines* establish "three criteria [that] must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance."

As demonstrated in the preceding sections, the overall results observed in the 34 epidemiologic studies are not attributable to chance and the association between ETS and lung cancer is not explained by bias or confounding.

Below, the evidence for a causal association between ETS and lung cancer is evaluated according to seven specific criteria for causality developed by an EPA workshop (U.S. EPA, 1989). These criteria are similar to the original and classical recommendations of Hill (1953, 1965). The seven recommended (but not official) criteria from the EPA workshop, which vary between essential and desirable, are listed below (U.S. EPA, 1989).

> A causal interpretation is enhanced for studies to the extent that they meet the criteria described below. None of these actually establishes causality; actual proof is rarely attainable when dealing with environmental carcinogens. The absence of any one or even several of the others does not prevent a causal interpretation. Only the first criterion (temporal relationship) is essential to a causal relationship: with that exception, none of the criteria should be considered as either necessary or sufficient in itself. The first six criteria apply to an individual study. The last criterion (coherence) applies to a consideration of all evidence in the entire body of knowledge.
>
> 1. Temporal relationship: The disease occurs within a biologically reasonable timeframe after the initial exposure to account for the specific health effect.
>
> 2. Consistency: When compared to several independent studies of a similar exposure in different populations, the study in question demonstrates a similar association which persists despite differing circumstances. This usually constitutes strong evidence for a causal interpretation (assuming the same bias or confounding is not also duplicated across studies).

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3. Strength of association: The greater the estimate of risk and the more precise, the more credible the causal association.

4. Dose-response or biologic gradient: An increase in the measure of effect is correlated positively with an increase in the exposure or estimated dose. If present, this characteristic should be weighted heavily in considering causality. However, the absence of a dose-response relationship should not be construed by itself as evidence of a lack of a causal relationship.

5. Specificity of the association: In the study in question, if a single exposure is associated with an excess risk of one or more cancers also found in other studies, it increases the likelihood of a causal interpretation.

6. Biological plausibility: The association makes sense in terms of biological knowledge. Information from toxicology, pharmacokinetics, genotoxicity, and in vitro studies should be considered.

7. Coherence: Coherence exists when a cause-and-effect interpretation is in logical agreement with what is known about the natural history and biology of the disease. A proposed association that conflicted with existing knowledge would have to be examined with particular care. (This criterion has been called "collateral evidence" previously.)

6.2. Assessment of Causality

We consider the extent to which the criteria for causality are satisfied for the ETS studies. Regarding *temporal relationship*, ETS exposure classification is typically based on the marital history of a subject, which varies, or on the status at the beginning of a prospective cohort study. Very few studies up through Tier 3 considered current exposure status only (see Appendix A), so some history of ETS exposure is largely the rule for ETS-exposed subjects. Analysis of data by exposure level in Section 3.3 indicates increased relative risk with exposure level, which supports the temporal relationship.

If ETS causes lung cancer, then the true relative risk is small for detection by epidemiologic standards and may differ between countries as well. However, by considering the totality of the evidence, it is determined that the large accumulation of epidemiologic evidence from independent sources in different locales and circumstances, under actual exposure conditions, is adequate for conclusiveness. Having accounted for variable study size, adjusted for a possible systematic spousal bias due to smoker misclassification, and considered potential bias, confounding, and other sources of uncertainty on a study-by-study basis, *consistency* of a significant association is clearly evident for the summary statistical measures for Tier 1 in Greece, Hong Kong, Japan, and the United States, and for Tiers 1 through 3 in the first three

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countries. There is too much obscurity and uncertainty attached to the studies in China for adequate data interpretation. Additionally, the evidence of increased risk of lung cancer at the highest exposure levels is consistent across countries.

The relative risks for each country are obtained by pooling estimates from the epidemiologic studies conducted in the country. The *strength of association* is limited by the true value of the relative risk, which is small. Statistical significance is attained, however, for the pooled studies of the United States and most other countries. The data were obtained from actual conditions of environmental exposure; therefore, imprecision is not increased by extrapolation of results from atypically high exposure concentrations, a common situation in risk analysis. Additionally, all studies were individually corrected for systematic bias from smoker misclassification at the outset, and qualitative characteristics of the studies were carefully reviewed to emphasize the results from the studies with higher utility for the objectives of this report. The outcome for the United States is heavily influenced by the large National Cancer Institute study (FONT) that was specifically designed and executed to avoid methodological problems that might undermine the accuracy or precision of the results.

Of the 17 studies reporting a test for upward trend, 12 are statistically significant at 0.05 (see Table 12) which would occur by chance alone with probability less than 10^{-9}. This evidence of *dose response* is very supportive of a causal interpretation because it would be an unlikely result of any operative sources of bias or confounding.

Specificity of effect is often cited as evidence of causality only with reservation, because specificity of an association supports a causal interpretation but lack of specificity does not negate it. To claim that ETS is "specific" to lung cancer in nonsmokers, it would be necessary to show that introduction of ETS causes lung cancer and removal of ETS is followed by the absence of lung cancer. But lung cancer has multiple causes, so specificity is not an applicable criterion. It may be noted that the specificity criterion also does not apply to active cigarette smoking as a cause of lung caner, for the same reason, yet there is widespread scientific and medical consensus that active smoking causes lung cancer.

Biomarkers such as cotinine/creatinine levels clearly indicate that ETS is taken up by the lungs of nonsmokers (see Fed. Reg., 1994). The similarity of carcinogens identified in sidestream and mainstream smoke, along with the established causal relationship between lung cancer and smoking in humans with high relative risks and dose-response relationships in four different lung cell types down to low exposure levels, provide *biological plausibility* that ETS is

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also a lung carcinogen. In addition, animal models and genotoxicity assays provide corroborating evidence for the carcinogenic potential of ETS. The epidemiologic data provide independent empirical verification of the anticipated risk of lung cancer from passive smoking and also an estimate of the increased risk of lung cancer to never-smoking women. The *coherence* of evidence from these approaches and the lack of significant arguments to the contrary strongly support causality as an explanation of the observed association between ETS exposure and lung cancer.

6.3. Conclusion

Based on the assessment of all the evidence of this report and in accordance with accepted guidelines and the causality criteria listed above for interpretation of human data, this report concludes that ETS is a carcinogen. Exposure of nonsmokers increases their risk of developing lung cancer.

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10. SUMMARY AND CONCLUSIONS

Thirteen epidemiologic studies have been reviewed and analyzed for evidence of increased risk of heart disease in never-smokers exposed passively to tobacco smoke. The number of studies is about equally divided between the prospective cohort type (7) and the retrospective case-control type (6). There are five cohort studies in the U.S. and one each in Japan and Scotland. The case-control studies are more scattered, with two in China and one each in Australia, England, Italy, and New Zealand. Thus the data are from a mix of cultural environments and lifestyles.

A review of each study was prepared that includes: (1) the author's abstract, (2) a study description, intended to highlight what was done, how it was done, and the outcome, and (3) comments, giving the reviewers' assessment of strengths and weaknesses regarding design, execution, data analysis, and interpretation. As far as possible the descriptive features of the studies were included in table format for easy comparison.

The statistical evidence of the 13 studies was analyzed from three perspectives: (1) comparison of those unexposed to ETS to those exposed at any level; (2) comparison to only those exposed at the highest level in each study; and (3) comparison across all exposure levels within a study for evidence of trend. Within each perspective, separate results were obtained by gender and by place of exposure (home or work).

For women, the epidemiologic evidence for exposure at home solidly supports the conclusion that passive exposure to tobacco smoke is associated with increased risk of heart disease morbidity and mortality in never-smoking women; the lesser amount of data for females exposed at work are consistent with that conclusion. The known risk factors for heart disease were reviewed and the studies were carefully analyzed for evidence of confounding that might inappropriately reduce or increase the relative risk due to ETS exposure when something else correlated with it is the actual cause. It was observed that the relative risk increased at least as often as it decreased when adjustment was made for other factors. As a further measure, comparisons were made at different levels of exposure within the same study to verify that the relative risk tended to increase with the level of exposure to ETS, which would be unlikely if ETS were not the causal agent. The possibility of partial confounding can never be totally eliminated but it appears unlikely, particularly when the analysis includes multiple independent studies conducted in a variety of environments with varying diets and other lifestyle characteristics.

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With fewer data and more mixed results, the evidence for males is less conclusive than for females. Men have a much higher mortality rate of heart disease than women in mid- and late-life, excluding smokers, so an equivalent increase in (absolute) mortality rate for women and men would appear as a much higher relative risk in women than men, and would thus be less detectable in men. The suggestive evidence of increased relative risk in males is consistent with the conclusions for females and should not be discounted without a biophysical explanation of why men should be at less risk of heart disease from ETS than women.

The criteria for causality from epidemiologic evidence have previously been described in Section 6.1 and the evidence assessed for lung cancer in Section 6.2. The assessment of causality for heart disease is similar in most respects to the assessment for lung cancer and, thus, will only be addressed briefly.

A *temporal relationship* between exposure and heart disease is apparent because exposure to ETS was ascertained for a period preceding occurrence of heart disease, regardless of whether the source of exposure was the tobacco smoke of the spouse, other household members, or coworkers. Studies differed in the duration of the exposure period taken into account, some only noting whether the subject is currently, or was ever, exposed.

Consistency of the association between ETS exposure and heart disease is supported by the overall assessment of studies conducted by numerous independent researchers on a mix of populations and cultures, using diverse study designs. Although there are numerous risk factors for heart disease which are difficult for any single study to take into account, the weight of evidence from all studies taken together strengthens the case that statistical associations between ETS exposure and heart disease are the result of causation.

Strength of the association is indicated by the validity and significance of the statistical outcome. Each study has been qualitatively reviewed (Appendix B), taking into account the potential for bias or confounding. Although some studies are relatively small or limited in other ways, there is sufficient evidence of high quality for reasonable assurance of the validity of the statistical results.

Dose-response data are available in three studies, which stratified exposure by amount or duration of spousal smoking. Two positive studies found a significant dose-effect, while one was borderline significant. Although the data are limited, this outcome strengthens the evidence of a causal relationship.

Specificity of effect is not an applicable criterion for heart disease and ETS because heart

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disease has numerous other causes. Lack of specificity of effect, however, does not negate ETS as a cause of heart disease.

Biological plausibility of ETS as a cause of heart disease follows from the evidence that active smoking causes heart disease and the qualitative similarity of sidestream smoke, the principal sources of ETS, and mainstream smoke. Additionally, experimental studies related to biophysical response to ETS and potential mechanisms leading to increased risk of heart disease support biological plausibility (Fed. Reg., 1994).

Coherence of the evidence is apparent from the statistical analyses of the epidemiologic data by different approaches, the information available on possible mechanisms, and the causative association between active smoking and heart disease.

It is the conclusion of this analysis that the evidence supports a causal relationship between ETS exposure and subsequent development of heart disease in nonsmokers.

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11. OCCUPATIONAL ANALYSIS: DESCRIPTION AND ANALYSIS OF EPIDEMIOLOGIC EVIDENCE

11.1. Introduction

The material on risk of lung cancer from ETS exposure in Chapters 1-6 focuses on exposure to spousal smoking. This chapter primarily summarizes the information available on workplace ETS exposure and risk of lung cancer in exposed nonsmokers from epidemiologic studies that appeared through October, 1993, supplementing the evidence in Chapters 1-6. Following tabulation and summarization of these data, the nature and quality of the epidemiologic evidence on the association between workplace ETS and lung cancer are discussed and conclusions are drawn regarding the strength of the evidence.

The analysis of data on risk of heart disease from ETS exposure in Chapters 7-10 already addresses exposure to ETS in the workplace in addition to exposure in the home. The evidence on risk of heart disease associated with workplace ETS is summarized along with the material on lung cancer in this chapter for the sake of completeness. Individual study descriptions on workplace ETS and the risk of lung cancer and heart disease are included in Appendix C.

Many of the same characteristics that apply to evaluations of spousal ETS exposure with disease outcome also apply when the evaluation shifts to workplace exposure. Several new tables are presented here which parallel tables compiled on lung cancer and spousal smoking. In particular, Table 26a corresponds to Tables 1 and 2, omitting most of the material (e.g., accrual period, references) that does not change for workplace exposure. Similarly, Tables 27a and 28 correspond to Tables 5 and 6, respectively, while Table 29a corresponds to Table 11. The information in Tables 3 and 4 applies equally well to workplace studies. Tables 14 and 15 already note the few minor differences for workplace analyses. Tables 26b, 27b, 29b, and 30b are the counterparts of Tables 26a, 27a, 29a, and 30a, except for heart disease instead of lung cancer.

11.2. Measures of Exposure and Risk

Workplace exposure to ETS is more difficult to assess than exposure from a smoking spouse. The presence of a smoking coworker, for example, provides no indication of intensity of exposure and subjects may not know the number of cigarettes or even the number of hours smoked per day by coworkers in their presence. The number of smoking coworkers also is an

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imperfect indicator of intensity since room size, ventilation, proximity of smokers, etc., are factors to be taken into account.

Evaluation of chronic health effects requires long-term exposure information, particularly for an endpoint such as lung cancer that has a long latency period. Exposure assessment is thus exacerbated by temporal changes in employment, coworker smoking habits, ventilation rate, and other factors. As a risk factor of only secondary interest in most studies (HE-II is a notable exception), efforts at determination of workplace exposure tend to be minimal and differ from those used to determine spousal exposure. Also, many studies employ substantial numbers of proxy respondents for deceased cases. Surviving spouses often serve as proxies and, while those proxies may serve as excellent sources of information about spousal ETS, their accuracy as sources of workplace exposure is questionable. Imprecise exposure estimates and resultant nondifferential misclassification may bias the results of workplace ETS studies toward the null hypothesis (no effect).

11.3. Overview of Available Data

11.3.1. *Lung Cancer*

The data available on lung cancer and exposure to workplace ETS are more limited than for exposure in the home. Of the 34 epidemiologic studies addressing ETS as a risk factor for lung cancer that have appeared to date, 19 provide data that may be helpful, either directly or indirectly. Those studies are listed in Table 26a, where each study is identified by the first four letters of the first author's surname. Case-control studies are listed first, followed by a single cohort study (BUTL(Coh)).

The studies represent diverse locales, including the U.S., Europe, and Asia. Half (9) of the studies are based on U.S. populations, while the rest are scattered between Hong Kong (2), China (2), and other countries. The number of individuals on which each study's primary workplace ETS analysis is based also varies widely, from under 100 (KOO and WU) to well over a thousand (BROW2). The prevalence of workplace ETS exposure also varies, but not as widely. The prevalence of exposure to occupational ETS is at least 40% for lung cancer cases and 35% for controls, except for GARF, among those studies for which data are available. At the extreme, several studies report exposure prevalences of over 70%, with most of the high exposures occurring among cases rather than controls (Table 26a). Tables 3 and 4 contain further descriptive characteristics applicable to the studies.

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Table 26a. Data applicable to workplace ETS and lung cancer.

Study	Country	Size[1]		% Workplace Exposure[2]	
		Cases	Controls	Cases	Controls
AKIB	Japan	*74*	*197*	57[3]	55[3]
BROW	United States	*102*[5]	*131*[5]	56[4]	38[4]
BROW2	United States	431	1166	•	•
BUFF	United States	— *938* —		•[5]	•[5]
CHAN	Hong Kong	84	139	40[6]	47[6]
FONT	United States	609	1247	63	61
GARF	United States	134	402	25[7]	29[7]
GENG	China	54	93	•[8]	•[8]
JANE	United States	191	191	•[8]	•[8]
KABA	United States	*78*[9]	*78*[9]	56[9]	54[9]
KALA	Greece	*89*	*118*	73	66
KOO	Hong Kong	*88*	*137*	75[10]	71[10]
LAMW	Hong Kong	60	144	72[6]	56[6]
LEE	England	*25*[11]	*256*[11]	40[11]	40[11]
SHIM	Japan	90	163	•	35
SVEN	Sweden	34	174	71[6]	66[6]
WU	United States	29[12]	62[12]	•	•
WUWI	China	415	602	55	50
BUTL (Coh)	United States	— *6467* —		•	•

[1]Number of subjects included in ETS analyses. Where numbers differ for workplace and spousal analyses, those relevant to workplace exposure are given and italicized; the corresponding numbers for spousal analyses can be found in Table 2.
[2]Percentage exposed at work unless otherwise noted.
[3]Exposure is employment outside the home vs. housewife.
[4]Includes active smokers as well as both genders. No raw data restricted to nonsmokers supplied.
[5]Total of 938 women included in analyses, 41% of whom were employed outside the home, but no precise breakdown by cases and controls was provided.
[6]Exposure at work, home, or both.
[7]During past 25 years. Percentages for past 5 years: cases 10.4%, controls 12.9%.
[8]Only risk estimates presented; no breakdown by cases and controls available.
[9]Males and females combined. 26 of 53 (31 of 53) female cases (controls) were exposed.
[10]Exposure only at work was too rare to yield meaningful estimates (2 cases and 4 controls so exposed).
[11]Both genders combined. 7 of 10 (58 of 98) male cases (controls) were exposed.
[12]Adenocarcinoma only.

• Data not available.

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Table 27a presents each study's crude and adjusted risk estimates (as available) for lung cancer with exposure to workplace ETS or the nearest relevant measure. Values for never-smokers are used to avoid potential distortion of estimates by active smoking. Crude estimates and confidence intervals were verified using raw data from the study wherever possible. Table 28 lists the risk estimates and the sources of exposure, as well as the potential confounding factors controlled for in the analysis and the statistical method(s) used. The risk estimate that employs the most direct workplace ETS measure and best demonstrates independence of other potential risk factors (through restriction to never-smokers and/or adjustment for other factors) is set off in boldface. Weighted means of the gender-specific risk estimates were computed for the few studies that presented separate results for males and females. Table 29a presents available data on linear trend, targeting never-smoking females to maximize comparability. Only six studies provide relevant information, with four of the six are from the U.S. Table 30a contains a summary of the study results on lung cancer by country.

11.3.2. *Heart Disease*

There are five studies that consider the relationship between occupational exposure to ETS and the development of heart disease (Table 26b) to varying degrees, with two cohort studies from the U. S. (BUTL(Coh) and SVEN(Coh)) and one case-control study each from Australia (DOBS), New Zealand (JACK), and China (HE-II). HE-II and SVEN(Coh) provide the most useful and detailed information for risk assessment. Both studies are of high quality and account for potential confounders (Table 22). SVEN(Coh) utilizes the data from MRFIT, which is a study of the effectiveness of intervention practices for males at high risk of coronary heart disease. Although the study is thorough, the participants are not representative of the working population of never-smokers that may be exposed at the workplace. HE-II is the only study where the principal objective is to study the association between heart disease and ETS exposure in the workplace. All of the participants are never-smoking ethnic Chinese women who are employed full time in Xi'an, China, and detailed data are provided on the extent of workplace exposure, using several different measures of exposure.

The estimated relative risk of heart disease from workplace ETS exposure in Table 24 is summarized in Table 27b. Each study's crude and adjusted risk estimates for exposure to workplace ETS are shown for comparison, except for SVEN(Coh), where only an adjusted relative risk is available. The information on adjustment factors for heart disease and the

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Table 27a. Estimated relative risk of lung cancer from workplace ETS by epidemiologic study.

Study	Never-Smokers	
	Crude RR[1, 2]	Adjusted RR[1, 2, 3]
AKIB	1.08[4] (0.69, 1.70)	1.97[4, 5] *
BROW	1.82[6, 7] (0.56, 5.88)	1.68[6, 7] (0.49, 5.50)
BROW2	*	0.6 - 1.2 *
BUFF	*	1.50[2, 4] *
CHAN	0.77 (0.49, 1.23)	*
FONT	1.12[8] (0.94, 1.32)	1.39[8] (1.15, 1.68)
GARF	0.93 (0.60, 1.43)	*
GENG	*	1.26 (0.85, 1.87)
JANE	*	0.91 (0.77, 1.09)[5, 16]
KABA	1.11[9] (0.65, 1.88)	*
KALA	1.70[10] (0.80, 3.62)	*
KOO	1.36[11] (0.59, 3.18)	*
LAMW	2.65[12] (1.56, 4.51)	*
LEE	0.99[13] (0.49, 2.00)	1.11[5] *
SHIM	*	1.2 *
SVEN	1.26[7] (0.65, 2.48)	1.4[5, 7] *
WU	*	1.3[14] (0.6, 2.8)

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 27a. (continued)

Study	Never-Smokers	
	Crude RR[1,2]	Adjusted RR[1,2,3]
WUWI	1.22 (0.99, 1.51)	1.1 (0.9, 1.5)
BUTL(Coh)	0.6[15] *	1.06[15] *

[1]Parentheses contain 90% confidence limits. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.
[2]RRs apply to exposure from smokers in the workplace, unless otherwise noted. BUFF includes active smokers, adjusting estimates for smoking status.
[3]Calculated by a statistical method that adjusts for other factors (see Table 22).
[4]Exposure is employment outside the home vs. housewife.
[5]Adjusted estimate is weighted average calculated from adjusted RRs for relevant exposed strata.
[6]Adenocarcinoma only. Data for crude RR values communicated from author (Brownson).
[7]Exposure at work and/or home.
[8]For adenocarcinoma alone, crude RR = 1.18 (90% CI 0.98, 1.42), adjusted RR = 1.46 (90% CI 1.19, 1.79).
[9]Both genders combined.
[10]Not including housewives. With housewives included among the unexposed, RR = 1.85 (90% CI 0.89, 3.85).
[11]Exposure at work and/or home RR = 1.24 (90% CI 0.74, 2.06).
[12]All cell types. For adenocarcinoma only, RR = 1.97 (90% CI 1.44, 3.40).
[13]Both genders combined. Crude RRs for males and females separately are 1.6 and 0.63, respectively.
[14]Adenocarcinoma only. Data on other cell types not restricted to nonsmokers.
[15]Both genders combined.
[16]Calculated from Table 17 of Varela (1987).

* Data not available.

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 28. Effect of statistical adjustments on lung cancer risk estimates for workplace ETS[1].

Study	Exposure		Crude	Adj.	Adjustment	Adjustment
	Source[2]	Place[3]	RR[4]	RR[4]	factor(s)[5]	technique[6]
AKIB	NS	NS	1.08	**1.97**	A, L, V	LR
BROW	A	P	1.82	**1.68**	A, I, O	LR
BROW2	A	W	*	**0.6-1.2**[8]	A, P, Sm	LR
BUFF	NS	NS	*	**1.50**[9]	Sm	S
BUTL (Coh)	A	W	0.6	**1.08**	A	LR
CHAN	A	H, W	**0.77**	*	*	*
FONT	A	W	1.12[10]	**1.39**[10]	A, E, I, L, R	LR
GARF	A	W	**0.93**[11]	*	*	*
	A	O	*	1.26[12]	A, H, SES, Yd	LR
GENG	Cw	W	*	**1.26**	Sm	LR
JANE	Cw	W	*	**0.91**[13]	A, G, I, L, M, Re	M, LR
	Cw	W	*	0.99/1.01[14]	A, G, I, L, M, Re, Sm[13]	M, LR
KABA	A	W	**1.11**[15]	*	*	*
	A	W	2.57/0.68[15]	*	*	*
KALA	Cw	W	**1.70**[16]	*	*	*
	Cw	W	*	1.08[17]	A, E, Ir	LR
KOO	A	W	**1.36/1.24**[18]	*	*	*
LAMW	Sp, Co Cw	A	**2.65**[19]	*	*	*
LEE	A	W	0.99[20]	**1.11**[20]	A	S
SHIM	A	W	*	**1.2**	A, H	M, LR
STOC	A	W	*[21]	*[21]	*	*
SVEN	A	H, W	1.26	**1.4**	A	S
	A	H, W[21]	1.1/1.8[22]	1.2/2.1[22]	A	S
WU	A	W	*	**1.3**[23]	A, L	M, LR
	A	W	*	1.23/2.3[24]	A, L, Sm	M, LR
WUWI	A	W	1.2	**1.1**	A, E, L	LR
	A	W	1.2[25]	1.2[25]	A, E, L, Sm	LR

[1]Values used for inference in this report are shown in boldface.

[2]Source: A = anyone; Co = cohabitant(s); Sp = spouse; Cw = coworker; NS = no specific ETS measure --employment outside the home is used as a marker of potential for ETS exposure at work.

[3]Place: A = anywhere; H = home/household; P = proximity of subjects; W = workplace; O = outside the home.

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Table 28. (continued)

[4]Odds ratio for case-control studies; relative risk for cohort studies.
[5]Adjustment factors: A = age of subject; E = education; H = hospital; I = income; Ir = interviewer; L = location; O = occupation of subject; R = racial or ethnic group; SES = socioeconomic status; Sm = active smoking; V = vital status; Yd = year of diagnosis; M = marital status; Re = religion.
[6]LR = logistic regression; R = regression; M = matched analysis; S = stratified.
[7]Including active smokers.
[8]Range of RRs for low-high exposure. No estimate for all exposed groups combined is available.
[9]Weighted average of RRs for occupations outside the home among all females, including smokers.
[10]All cell types. For adenocarcinoma alone, RR = 1.18 crude, 1.47 adjusted.
[11]Exposed during last 25 years. For last 5 years, RR = 0.88.
[12]Estimated relative risk for exposure to 20 cig./day from logistic regression model. Regression coefficient was 0.012 (SE 0.010).
[13]Male and female never-smokers only.
[14]Never-smokers plus former smokers who quit at least 10 years ago. First RR is for all subjects; second RR is for self-respondents only. Active smoking adjustment refers to former smoking.
[15]1.11 is for both genders combined; RR = 2.57 for males, 0.68 for females.
[16]"Some" vs. "minimal" exposure at work. With housewives included in "minimal" work exposure group, RR = 1.85.
[17]RR for highest quartile of workplace exposure from regression model utilizing number of years x number of smokers as independent variable. No other quartile exposure data provided.
[18]Exposure at work or both work and home/exposure at work, home, or both. Restricted to nonsmokers. RRs higher for active smokers, e.g., 3.23 for work and/or home.
[19]All cell types. For adenocarcinoma alone, RR = 1.97 for all ETS sources combined, 2.01 for spousal ETS. No spousal ETS data for non-adenocarcinoma.
[20]Exposed at all at work vs. not at all. Adjusted estimate is weighted mean of adjusted RRs for all exposed strata. All estimates are for both genders combined. Crude (adjusted) RR for males = 1.6 (2.0), for females = 0.6 (0.7).
[21]No data available. Reported no statistically significant increase in RR.
[22]Exposed at either home *or* work, but not both/exposed both at home *and* work.
[23]Adenocarcinoma only.
[24]Adenocarcinoma/squamous cell cancer. Active smokers included.
[25]Includes active smokers.

* Data not available.

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 29a. Exposure response trends for workplace ETS and lung cancer.

Study	Case	Cont.	Exposure[1]	RR[2]	C. I.[2]	P-trend[3]
BROW2[4]	*	*	No	1.0		*
(hours/day x years)	*	*	Low	0.6	(0.4, 0.8)	
	*	*	Medium	0.7	(0.4, 0.9)	
	*	*	High	1.2	(0.9, 1.6)	
BUTL (Coh)	*	*	0	1.0		0.76
(years)	*	*	1-10	1.0	(0.07, 6.4)	
	*	*	> 10	1.4	(0.08, 8.9)	
FONT[5]	224	491	0	1.0		0.001
(years)	213	450	1-15	1.30	(1.05, 1.60)	
	118	223	16-30	1.40	(1.09, 1.79)	
	54	83	> 30	1.86	(1.32, 2.61)	
JANE	*	*	Model[6]	-0. 01[6]	*	0.98
(smokers x years/smoker)						
KALA	24	40	Housewife	1.00[7]		0.07
(smokers x years)	52	68	Minimal	1.27[7]	(0.76, 2.15)	
	13	10	Some	2.17[7]	(0.96, 4.88)	
LEE	36	339	None	1.00	*	*
(subjective estimate)	5	67	Little	1.82	*	
	1	48	Average +	0.19	*	

[1]Workplace ETS.
[2]Adjusted RR estimate and confidence interval drawn from source wherever possible (95% confidence intervals were converted to 90% confidence intervals). When not available, crude estimates are used.
[3]P-value for trend; halved for studies providing two-sided p-value.
[4]Risk estimates communicated by author (Brownson).
[5]All lung cancers. Trend upward but not as strong (p=0.10) for adenocarcinoma only. Raw numbers communicated by author (Fontham).
[6]Logistic regression model used to provide slope estimate (-0.01) indicates slight downward trend. ORs across 8 exposure categories ranged from 0.47 to 1.19 with no dose-response.
[7]Crude ORs. Adjusted OR from regression model said to be 1.08 (90% C.I. 0.31, 3.82) for "extreme quartiles" of workplace ETS exposure, but no further data provided.

* Data not available.

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 30a. Workplace ETS study results for lung cancer by country.

Country	Study	Workplace Specific?[1]	Primary risk estimate[2]	P-value for trend
Greece	KALA	Y	1.08/1.70[3]	0.07
Hong Kong	KOO	Y	1.36[4]	*
Hong Kong	LAMW	N	2.65[4]	*
Japan	AKIB	N	1.97	*
Japan	SHIM	Y	1.2	*
USA	FONT	Y	1.39	0.001
USA	BROW2	Y	0.6-1.2[5]	ns
USA	BUTL (Coh)	Y	1.10	ns
USA	GARF	Y	0.93[4]	*
USA	JANE	Y	0.91	ns
USA	KABA	Y	1.11[4]	*
USA	WU	Y	1.3	*
USA	BROW	Y	1.68	*
USA	BUFF	N	1.50	*
W. Europe				
Eng./Wales	LEE	Y	1.11	ns
Sweden	SVEN	N	1.4	*
China	CHAN	N	0.77[4]	*
China	GENG	Y	1.26[4]	*
China	WUWI	Y	1.1	*

[1]Study reported results specifically addressing workplace ETS exposure, Y = yes, N = no. More detailed description of exposure sources is in Table 28.

[2]Ever exposed to workplace ETS compared to never exposed. Age-adjusted estimates presented unless otherwise noted; factors adjusted for are listed in Table 28.

[3]Adjusted estimate of 1.08 contrasts two exposure quartiles; crude estimate of 1.70 contrasts ever and never exposed.

[4]Crude estimate.

[5]Range of RRs for exposed groups. No combined estimate available.

* Data not available; ns = not statistically significant.

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Table 26b. Data applicable to workplace ETS and heart disease.

Study	Gender	Endpoint[1]	Country	Size[2] Cases	Size[2] Controls	% Workplace Exposure Cases	% Workplace Exposure Controls
BUTL	M	IHD(F)	USA	75	1,489	--- 41.4[4] ---	
(Coh)[3]	F			70	3,488	--- 43.4[4] ---	
DOBS[5]	M	MI(F+N) + CD(F)	Australia	75	205	36.0	38.5
	F			17	197	29.0	37.1
HE-II	F	CHD(N) =MI(N)+ANG(N)	China	59	126	56	34
JACK[6]	M	CHD(F)	New	21	61	43	36
	F		Zealand	9	62	33	21
	M	MI(F)		28	123	43	31
	F			11	112	27	22
SVEN (Coh)	M	CHD(F)	USA	*	1,237	--- 73.2 ---	
		CHD(F+N)		*	1,237	--- 73.2 ---	

[1]F (fatal), N (nonfatal). See key in footnote 4 of Table 19.
[2]For cohort studies, entry under "cont." refers to referent group; entry under "case" is the number of cases that occurred.
[3]For the AHSMOG cohort of current non-smokers (includes former smokers), a subset of non-hispanic whites.
[4]Based on person-years.
[5]Includes only the subjects with jobs outside the home.
[6]Number of cases and controls may be overstated. Some subjects were subsequently excluded who did not meet inclusion criteria.

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 27b. Estimated relative risk of heart disease from workplace ETS by epidemiologic study.

Study	Gender	Endpoint	Never-Smokers	
			Crude RR[1]	Adjusted RR[1,2]
BUTL (Coh)[3]	M	IHD(F)	0.60	1.04[4]
			(0.39, 0.91)	(0.7, 1.6)
	F		0.78	1.85[4]
			(0.52, 1.17)	(1.2, 2.8)
DOBS	M	MI(F+N) +	0.90	0.95
	F	CD(F)	(0.55, 1.46)	(0.56, 1.61)
			0.71	0.66
			(0.23, 1.88)	(0.21, 2.10)
HE-II	F	CHD(N)	2.45	1.85
		=MI(N)+ANG(N)	(1.37, 4.37)	(0.97, 3.53)
JACK	M	CHD(F)	1.3	1.8
			(0.6, 3.1)	(0.8, 4.2)[5]
	F		3.6	2.2
			(0.9, 15.2)	(0.5, 9.3)[5]
	M	MI(F)	1.7	1.8
			(0.8, 3.5)	(0.8, 3.7)[5]
	F		1.4	1.1
			(0.4, 6.2)	(0.3, 4.8)[5]
SVEN (Coh)	M	CHD(F)	*	2.6
				(0.7, 9.8)
		CHD(F+N)	*	1.4
				(0.9, 2.3)

[1]Parentheses contain 90% confidence limits. Odds ratios are shown for case-control studies; relative risks are shown for cohort studies.
[2]Calculated by a statistical method that adjusts for other factors (see Table 22).
[3]AHSMOG cohort.
[4]Former smokers included, with no adjustment of results for former smoking.
[5]Estimated by multiplying the confidence interval for the crude RR by the ratio of adjusted RR to crude RR.

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statistical techniques used, as displayed in Table 28 for lung cancer, is extensively detailed in Table 22. The data and analysis on exposure trends for heart disease in Table 25 are summarized in Table 29b. The results for heart disease are summarized by country in Table 30b.

11.4. Results on Lung Cancer

11.4.1. *Overview of Results*

The prevalence of exposure to ETS in the workplace is higher for cases than controls in nine of the 12 studies for which figures are available, lower in two studies (CHAN and GARF), and equal in one (LEE) (Table 26a). The crude relative risk is above the null (i.e., RR < 1) in nine studies, a little below the null in two studies (GARF and LEE), and well below the null in two more studies (CHAN and BUTL(Coh)). Adjusting for cofactors increases the relative risk more often than it decreases it. Of the seven studies where crude and adjusted relative risks are both available, adjusting for cofactors raises the relative risk in five studies (AKIB, 1.08 to 1.97; FONT, 1.12 to 1.39; LEE, 0.99 to 1.11; SVEN(Coh), 1.26 to 1.4; and BUTL(Coh), 0.6 to 1.06), compared to lowering it a small amount in two studies (BROW, 1.8 to 1.7; WUWI, 1.2 to 1.1) (Table 27a). Overall, confounding appears unlikely.

A total of 19 studies present one or more adjusted risk estimates for measures relevant to workplace ETS exposure (workplace specific, inclusive, or surrogate). Primary estimates (indicated by boldface in Table 28) for ever-exposed vs. never-exposed are elevated in 15 of these studies, ranging from 1.08 (KALA) to 1.97 (AKIB) for nonsmoking females. Of the remaining studies, only the relative risk for CHAN falls below 0.91, and this decrease is not statistically significant. Where studies provide analyses for males as well as females (BUTL(Coh), KABA, LEE), results are inconsistent. BUTL(Coh) found an adjusted relative risk of 0.95 for males and 1.18 for females, while the adjusted relative risks of KABA and LEE are higher for males than females (2.6 to 0.7, and 2.0 to 0.7, respectively). Weighted averages of the gender-specific estimates for those studies, however, are all above 1.0: 1.10, 1.11, and 1.11 for BUTL(Coh), KABA, and LEE, respectively.

11.4.2. *Results by Type of Exposure*

Studies on lung cancer will be discussed further according to the type of exposure employed, including those with data on job status only, those with mixed-source data, and those with separate data on workplace sources.

Two studies (AKIB and BUFF) present data on employment status outside the home, and

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Table 29b. Exposure-response trends for workplace ETS and heart disease.

Study	Gender	Case	Cont.	Exposure[1]	RR[2]	C.I.[2]	P-trend[3]
BUTL (Coh)	M	53	7,999[4]	0[5]	1.00		
(years)		13	3,160[4]	1-10	1.26	(0.75, 2.11)	
		9	2,420[4]	11+	0.76	(0.42, 1.38)	>0.5
(years)	F	44	13,870[4]	0[5]	1.00		
		13	5,802[4]	1-10	1.85	(1.10, 3.11)	
		13	4,670[4]	11+	1.86	(1.10, 3.15)	>0.5[9]
HE-II	F	26	83	0-5[6]	1.00		
(cig/day)		10	25	6-10	0.87	(0.36, 2.13)	
		15	14	11-19	2.95	(1.24, 7.01)	
		8	4	20+	3.56	(1.03, 12.29)	0.01
(years)		26	83	0-5[5]	1.00		
		8	12	6-15	3.08	(1.10, 8.68)	
		25	31	16+	1.56	(0.77, 3.18)	0.06
(no. smokers)		26	83	0[7]	1.00		
		16	36	1-2	1.16	(0.55, 2.44)	
		12	6	3	5.06	(1.74, 14.69)	
		5	1	4+	4.11	(0.57, 29.88)	0.01
(total expos.)		26	83	0[8]	1.00		
		13	32	1-2000	1.00	(0.45, 2.21)	
		5	8	2001-4000	2.05	(0.60, 7.01)	
		15	3	4001+	9.23	(2.57, 33.09)	0.003

[1]Workplace ETS
[2]Adjusted RR estimate and 90% confidence interval taken from source wherever possible (95% confidence intervals were converted to 90% confidence intervals). When not available, crude estimates are used.
[3]P-value for trend; halved for studies providing two-sided p-value.
[4]Person-years. Exposure-response trend data only available for AHSMOG cohort. Results include former smokers.
[5]Years of exposure.
[6]Cig./day.
[7]Number of smokers.
[8]Total exposure (cig./day x years x smokers x hours/100).
[9]Calculation based on crude data. Adjusted RRs shown suggest an upward trend.

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Source: https://www.industrydocuments.ucsf.edu/docs/qhfl0000

Table 30b. Workplace ETS study results for heart disease by country.

Country	Study	Gender	Endpoint	Primary risk estimate[1]	P-value for trend
China	HE-II	F	CHD(N)	1.85	0.01[2]
USA	BUTL (Coh)	M	IHD(F)	1.04[3]	>0.5
USA		F		1.85[3]	>0.5
USA	SVEN (Coh)	M	CHD(F)	2.6	*
USA			CHD(F+N)	1.4	*
Australia	DOBS	M	MI(F+N)+CD(	0.95	*
Australia		F	F)	0.66	*
New Zealand	JACK	M	CHD(F)	1.8	*
New Zealand		F		2.2	*
New Zealand		M	M(F)	1.8	*
New Zealand		F		1.1	*

[1]Exposed to workplace ETS compared to unexposed. Age-adjusted estimates presented unless otherwise noted; factors adjusted for are listed in Table 22.
[2]Exposure metric is cigarettes smoked per day by coworkers. For other measures of exposure see Table 29b.
[3]AHSMOG cohort. Former smokers included, with no adjustment of results for former smoking.

* Data not available.

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both studies observed an increased risk associated with employment: adjusted RR = 1.97 in AKIB, 1.50 in BUFF (no confidence intervals available). The observation of elevated relative risks for women employed outside the home compared to housewives is the outcome expected if workplace ETS exposure does increase risk of lung cancer. Four studies collected information on workplace ETS but presented only data that included exposure on the job as one component of an index embracing other sources of exposure as well. BROW reported a relative risk of 1.7 (90% CI 0.5, 5.5) for four or more hours/day spent in the presence of a smoker in any setting. CHAN and SVEN(Coh) analyzed exposure at home and/or work to yield relative risks of 0.8 (90% CI 0.5, 1.2) and 1.4 (no CI available), respectively, while data from LAMW produced a relative risk of 2.7 (90% CI 1.6, 4.5) for the same measure. Fourteen studies permit analyses based on measures of exposure specific to the workplace. Of 14 workplace-specific studies, all but three produce risk estimates above the null, a pattern not likely due to chance ($p=0.046$). Of the three below-null studies, GARF presents only crude results, and BROW2 reports a mildly elevated relative risk at high exposure.

Two workplace specific studies (FONT and KALA) took particular care to minimize the potential for bias, based on characteristics of study design and methodology. Both studies yielded relative risks above the null: RR = 1.39 (90% CI 1.15, 1.68) for FONT and 1.08 (no CI available) for KALA. However, the only adjusted relative risk available from KALA compares two exposure quartiles rather than presenting a comparison of ever and never exposed. Only a crude estimate was available for the latter comparison (RR = 1.70, 90% CI 0.80, 3.62). FONT also found a statistically significant upward trend ($p = 0.001$, Table 29a). At the other extreme, two workplace specific studies (GENG and WUWI) have large potential for bias so their results on lung cancer carry little weight (see reviews in Appendix A and Appendix C). The relative risks of GENG and WUWI are 1.26 and 1.1, respectively. Of the remaining nine workplace-specific studies, six have relative risks above the null (BUTL(Coh), KABA, KOO, LEE, SHIM, WU; see Table 27a for confidence intervals), one (BROW2) has mixed evidence (RR = 0.6-1.2, no CI available), and two (GARF and JANE) have estimates below the null (RR = 0.93, 90% CI 0.60, 1.43; and RR = 0.91, 90% CI 0.80, 1.04, respectively).

11.4.3. *Results by Country*

Comparisons within and between countries are somewhat varied. All three workplace-specific studies on Asian populations (SHIM from Japan, GENG and WUWI from China) report

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mildly elevated relative risks ranging from 1.1 to 1.26. The two workplace-specific studies on European populations (KALA and LEE) observed elevated relative risks in both Greek (KALA, crude RR = 1.7) and English (LEE, adjusted RR = 1.11) populations. Within the U.S., however, the workplace-specific studies produced mixed results. BROW, BUTL(Coh), FONT, KABA, and WU observed ever-exposure relative risks above the null (1.7, 1.1, 1.4, 1.1, and 1.3, respectively), while GARF and JANE reported relative risks below the null (both 0.9) and BROW2 reported results by exposure level that fell on either side of the null (0.6-1.2).

Most studies include only females, but KABA and JANE include both genders. In KABA, the relative risk is high for males (2.6) but low for females (0.7), leaving a value of 1.11 for both genders combined. JANE, in contrast, reports a slightly depressed relative risk for both genders combined, but gender-specific results are not available. One of the two studies with below-null results lacked adjustment for age (GARF), compared to one out of five with above-null results (KABA).

Dose-response data for workplace ETS exposure are sparse. Only six studies present relevant information, and one of these (LEE) employs a subjectively estimated, though workplace-specific, exposure index. Three studies provide indications of an upward trend in response among females; while the rest provide little or no indication of such a trend (Table 29a). The few studies which did not find higher relative risks for comparison of ever-exposed with never-exposed are over-represented among the studies with dose-response data, and some of the stratum-specific relative risks are highly unstable. Overall, the data for analysis of trend or dose-response are too limited in quantity and quality to be very informative.

11.5. Results on heart disease

There are only five studies with data on exposure in the workplace, with a mix of fatal and nonfatal endpoints (Table 26b). The prevalence of occupational exposure varies widely across the studies, in part because of different criteria for classifying persons as exposed or unexposed. In the only study with detailed occupational exposure data (HE-II), the prevalence of exposure at work is about 50% higher for cases than controls (56% vs. 34%). The crude relative risk exceeds the null in HE-II and is consistently above the null for both genders and endpoints in JACK, a very small study, but is below the null for both genders in BUTL(Coh) and DOBS.

Adjusting for cofactors increases the relative risk in about half the outcomes and decreases it in the other half. The adjustment in BUTL(Coh) is for age alone, which increases the relative risk

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to a significantly high value of 1.85 for females, although former smokers are included in the analysis. There is little effect in DOBS, which adjusts for age and personal history. Adjustment increases the relative risk for males but decreases it for females in JACK, but the sample sizes are small with wide confidence intervals. He-II adjusts the crude relative risk for a large number of factors, which reduces it from 2.45 to 1.85. Unknown correlations between workplace ETS and adjustment factors limit the interpretation of the difference between crude relative risks and adjusted relative risks. In the case of HE-II, the relative risks at the highest exposure values alone and the evidence of upward linear trend are supportive of an association between workplace ETS and heart disease (Tables 25 and 29b). Overall, the effect of adjusting for cofactors is varied and the number of studies is too small and the endpoints too mixed to discern any general patterns in the effect of adjusting for cofactors.

In DOBS, JACK, and SVEN(Coh), the study participants are simply dichotomized as exposed or unexposed to ETS at work, depending on the questions asked. BUTL(Coh) groups participants according to the number of cigarettes to which they are exposed. HE-II utilizes several indicators of workplace exposure (cigarettes/day, years, number of smokers, and cumulative exposure), which not only allows for tests of trend but also for comparison of results for robustness to the index of workplace exposure used.

BUTL(Coh) gives no indication of an association between workplace ETS and heart disease for males (RR = 1.04, 90% CI 0.7, 1.7) but finds a significant association for females (RR = 1.85, 90% CI 1.2, 2.8) with one-sided p = 0.04 (Table 24). The relative risks are below the null in DOBS for both males and females, and widely mixed in JACK, but the estimates are unstable due to the small study and thus not very informative. The relative risk is elevated in SVEN(Coh) for fatal CHD, but the sample size is quite small; when nonfatal incidents are included to enlarge the sample size, the relative risk is 1.4 (90% CI 0.9, 2.3) with one-sided p = 0.13. For HE-II, RR = 1.85 (90% CI 0.97, 3.53), with one-sided p = 0.06 for exposure at work but not at home, which increases to RR = 2.36 (90% CI 1.37, 4.37), with one-sided p = 0.02 when exposure includes home and/or work.

At the highest exposure only, BUTL(Coh) is significant for females (one-sided p = 0.03) but not for males ($p > 0.5$), and HE-II, which includes females only, is very significant ($p = 0.001$) (Table 25). The data for females in BUTL(Coh) suggests an upward trend but no p-value is available, while there is no evidence of trend for males (Table 25 and Table 29b). In HE-II, the evidence of trend is robust across difference measures of exposure to ETS in the workplace (cig./day, p = 0.01; years, p = 0.06; number of smokers, p = 0.01; total exposure, p = 0.003) (Tables 25 and 29b).

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11.6. Summary and conclusions

The study results for lung cancer are summarized by country in Table 30a. Tests for trend are available in only six studies, with two, KALA and FONT, providing evidence of an upward trend ($p = 0.07$ and 0.001, respectively). Without discounting the other four studies, KALA and FONT are particularly high quality studies (see reviews in Appendices A and C). FONT is the premiere data source on workplace ETS and lung cancer in the United States. In addition to significance for trend, the relative risk in FONT for exposed versus non-exposed in the workplace is significant (RR = 1.39, $p<0.01$).

A preponderance of the observed relative risks for lung cancer in Table 30a are in the direction of a positive association between workplace exposure to ETS and occurrence of lung cancer. An excess risk of lung cancer is reported in 11 of the 14 studies with workplace-specific measures of ETS and in four of the five with only indirect indicators of occupational exposure. For workplace-specific studies, risk estimates range from 0.91 to 1.40, with most (11 of 14) between 1.1 and 1.39. The probability of 11 or more positive studies out of 14, by chance alone, is only 0.03.

Of the 14 studies with workplace-specific measures of ETS, the three with relative risks for lung cancer below the null (GARF, JANE, and BROW2) are from the total of eight in the U. S., although the results from BROW2, the largest U. S. study, are equivocal (only a range is available for the relative risk, from 0.6 to 1.2). The relative risk exceeds the null in the remaining six studies conducted in other countries. The greater variability of outcomes within the U. S. relative to other countries may be due to some extent to: cultural differences related to exposure in the workplace, particularly job mobility; concordance with ETS exposure at work and elsewhere, particularly in the home; or other risk factors for lung cancer. Additionally, variability in study outcomes should be expected even within a single country, such as the U. S., because of: the uncertainty in intensity and duration of exposure to workplace ETS; the likelihood of high variability of exposure and possibly susceptibility to lung cancer *within*, as well as *between*, the exposed and unexposed groups; and the likelihood that any excess risk from exposure to workplace ETS alone is small, limiting the statistical power for detection.

Overall, the data on occupational exposure to ETS contribute to the total body of evidence on ETS and lung cancer, and support the prior conclusion based on studies in the home that exposure to ETS increases the risk of lung cancer in nonsmokers. Although reassuring, that outcome would be anticipated since there is no reason to believe that ETS would be a risk factor for lung cancer in one environment, such as the home, but not in another, such as the workplace.

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The data on heart disease and workplace ETS are relatively limited compared to the data on exposure in the home. There are only five studies on workplace exposure, consisting of two cohort studies in the U. S. (BUTL(Coh) and SVEN(Coh)) and three case-control studies in other countries (DOBS, Australia; JACK, New Zealand; and HE-II, Xi'an, China). The adjusted relative risks are below the null for both genders in DOBS, but consistently above the null otherwise. Some care needs to be taken not to double-count outcomes within the same study though, as JACK uses the same controls for both outcomes (CHD(F) and MI(F)), and SVEN(Coh) reports relative risks for both CHD(F) and CHD(F+N), although the same data are used in both except for the addition of nonfatal outcomes to the latter. The increased relative risk is significant for females in BUTL(Coh) (one-sided $p = 0.04$). In HE-II, the one-sided significance level is 0.02 for ETS exposure in the home, workplace, or both, and 0.06 for exposure at work alone. HE-II, the only study with a test for trend, provides substantial evidence of an increase in heart disease with the level of exposure to workplace ETS. HE-II is particularly noteworthy because it is the only study where occupational exposure is the principal objective and it is a particularly high quality study as well (see reviews in Appendix B and Appendix C).

As with lung cancer, the data on heart disease and occupational exposure to ETS are part of the total evidence that includes studies of exposure in the home as well. The limited data on workplace ETS is suggestive, but not conclusive by itself, of increased risk of heart disease from exposure to ETS. HE-II is a solid supportive study, but workplace ETS is addressed secondarily to household exposure in the four remaining studies. The data on workplace exposure strengthen the evidence from the larger body of data on household exposure that ETS increases the risk of heart disease in nonsmokers. There is no evidence to suggest that the place of exposure, such as work, home, or elsewhere, should be consequential.

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